Oath/Declaration

The Oath/Declaration was objected to because it lacked the signature of one of the inventors. Applicants submit herewith a new executed Oath/Declaration. Accordingly, Applicants respectfully request reconsideration and withdrawal of this objection.

Objection to the Claims

Claims 2, 3, 5-7, 9-14, 17-19 were objected to because they depend from a rejected claim but would be allowable if rewritten as independent claims incorporating the limitations of the parent claim(s).

In view of the present amendment of independent claim 1 Applicants respectfully submit that this objection has been rendered moot.

Rejection of Claim 14 Under 35 U.S.C. §101

Claims 1, 4, 8, 16, 16, 20 and 25 have been rejected as being "directed toward non-statutory subject matter because human beings can be considered to be compositions of matter comprising nucleic acids with characteristic[s] set forth in these claims (Paper No. 26, p. 2)."

Applicants have amended independent claim 1, from which the remainder of the above-identified rejected claims depend, to specify that the claimed subject matter is an isolated composition comprising the specified nucleic acid molecules with the particular characteristics. Accordingly, Applicants respectfully submit that the claims as amended comply with thte requirements of 35 U.S.C. §101 and request reconsideration and withdrawal of the foregoing rejection.

Rejection of Claims 1-13 and 20-24 Under 35 U.S.C. §112, First Paragraph

Claims 22 and 23 were rejected because the specification, "***while being enabling for in vitro methods of introducing nucleic acid constructs encoding an antitumor agent into a cell,*** and for *in vivo* methods of introducing such constructs directly into cells of a tumor, does not reasonably provide enablement for *in vivo* methods of introducing nucleic acid constructs into all cells by any delivery route as broadly claimed" (Paper No. 26, p. 4).

Applicants traverse this rejection, and respectfully assert that the model used by Lipinski *et al.* (2001) is a well-accepted tumor model. Moreover, the date generated clearly show successful reduction of tumor mass upon systematic introduction of claimed composition, thereby providing sufficient evidence of efficient delivery of the gene at therapeutic levels using methods disclosed in the instant specification. However, in order to expedite prosecution claim 22 has now been amended to limit the claims to *in vitro* methods. As indicated in the Office Action (see bold and italic section above), such *in vitro* methods have been deemed enabled by the instant specification. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

Rejection of Claims 22 and 23 Under 35 U.S.C. §112, Second Paragraph

Claims 22 and 23 have been rejected under 35 U.S.C. §112, second paragraph as, "being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Specifically, the Office Action states that, "claims 22 and 23 are indefinite because they fail to recite any intended outcome of the method, so it is unclear what method/process applicant is intending to encompass" (Paper 26, p. 13).

Applicants have amended the claims to specify the process of controlling the proliferation of a tumor cell, thereby rendering the foregoing rejection moot. Accordingly, Applicants respectfully request reconsideration and withdrawal of the foregoing rejection.

Rejection of Claims Under 35 U.S.C. §102(b)

Claims 1, 4, 8, 15, 16, 20, 21, and 25 have been rejected as being anticipated by Symonds et al., on the grounds that, "Symonds teaches a cell (a composition) comprising wild type p53 gene and an HSP70 gene. Absent evidence to the contrary these genes comprise a p53 promoter and an HSP70 promoter respectively. The HSP70 gene corresponds to the first nucleic acid construct of the claims, whereas the p53 gene corresponds to the second nucleic acid construct of the claims" (Paper 26, p. 14).

Claims 1, 4, 6, 12, 16, and 20-25 25 were further objected as being anticipated by Yamaguchi et al., on the grounds that, " Yamaguchi teaches neuroblastoma cell comprising both a plasmid vector encoding the PCNA promoter operably linked to a CAT reporter gene, and a

plasmid vector encoding wild type p53 operably linked to a CMV promoter" (Paper No. 26, p. 15).

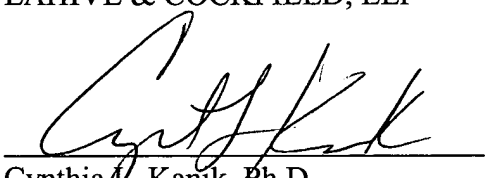
In the interest of expediting prosecution, and without acquiescing to the rejection, Applicants have amended the claims to specify that the first gene encodes an antitumor agent. Accordingly, Applicants respectfully submit that the Symonds and Yamaguchi references do not anticipate the claims as amended. Accordingly, Applicants respectfully request reconsideration and withdrawal of the foregoing rejection.

CONCLUSION

On the basis of the foregoing amendments and remarks, Applicants respectfully submit that the pending claims are in condition for allowance. If a telephone conversation with Applicants' Attorney would expedite prosecution of the above-identified application, the Examiner is invited to call the undersigned at (617) 227-7400.

Respectfully submitted,

LAHIVE & COCKFIELD, LLP



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APPENDIX A

VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. **(Amended)** A composition comprising a first nucleic acid construct comprising a first gene encoding an antitumor agent whose expression is controlled by a first promoter whose function is suppressed by a wild-type p53 or $p16^{INK4}$ allele in non-tumor cells relative to tumor cells carrying a mutant p53 or p16 allele, and a second nucleic acid construct comprising a second gene whose gene product suppresses expression of said first gene, wherein the expression of said second gene is controlled by a second promoter that is up-regulated in non-tumor cells relative to tumor cells carrying a mutant p53 or p16 allele, such that said first gene is expressed in tumor cells and suppressed in non-tumor cells.

22. **(Amended)** A method of controlling the proliferation of a tumor cell comprising introduction of a first nucleic acid construct and a second nucleic acid construct of ~~a~~ the composition according to claim 1 into ~~a~~ the cell *in vitro*.

APPENDIX B

PENDING CLAIMS

1. An isolated composition comprising a first nucleic acid construct comprising a first gene whose expression is controlled by a first promoter whose function is suppressed by a wild-type p53 or $p16^{INK4}$ allele in non-tumor cells relative to tumor cells carrying a mutant p53 or p16 allele, wherein said first gene encodes an antitumor agent, and a second nucleic acid construct comprising a second gene whose gene product suppresses expression of said first gene, wherein the expression of said second gene is controlled by a second promoter that is up-regulated in non-tumor cells relative to tumor cells carrying a mutant p53 or p16 allele, such that said first gene is expressed in tumor cells and suppressed in non-tumor cells.

2. The composition according to claim 1 wherein said second gene of said second nucleic acid construct encodes an antisense RNA transcript complementary to a sequence within mRNA encoded by said first gene of said first nucleic acid construct.

3. The composition according to claim 1 wherein said second gene of said second nucleic acid construct encodes a ribozyme specific for a sequence within mRNA encoded by said first gene of said first nucleic acid construct.

4. The composition according to claim 1 wherein said second gene of said second nucleic acid construct encodes a sequence-specific transcriptional suppressor and said first nucleic acid construct comprises a binding site recognized by said sequence-specific transcriptional suppressor.

5. The composition according to claim 4 wherein said sequence-specific transcriptional suppressor is a *lac* operator suppressor.

6. The composition according to claim 4 wherein said sequence-specific transcriptional suppressor comprises a *tet* repressor DNA-binding domain and a transcriptional suppression domain of the *Drosphilia* KRAB transcription factor.

7. The composition according to claim 4 wherein said sequence-specific transcriptional suppressor comprises a Gal-4 DNA-binding domain and a transcriptional suppression domain of the *Drosphilia even-skipped* transcription factor.

8. The composition according to claim 1 wherein said first nucleic acid construct and said second nucleic acid construct are each on separate nucleic acid vectors.

9. The composition according to claim 1 wherein said first nucleic acid construct and said second nucleic acid construct are on a single nucleic acid vector.

10. The composition according to claim 9 comprising an insulator sequence between said first nucleic acid construct and said second nucleic acid construct.

11. The composition according to claim 10 wherein said nucleic acid vector is a viral vector.

12. The composition according to claim 1 wherein said second promoter of said second nucleic acid construct comprises a p53 binding site sequence or CMV promoter.

13. The composition according to claim 12 wherein said second nucleic acid construct comprises said p53 binding site sequence downstream of a TATA Box and downstream of the transcriptional start site of said second promoter of said second nucleic acid construct.

15. The composition according to claim 1 wherein said first promoter is the HSP70 promoter.

18. The composition according to claim 17 wherein said antitumour agent is a pro-drug activating enzyme.

19. The composition according to claim 18 wherein said pro-drug activating enzyme is a thymidine kinase.

20. A cell containing a first nucleic acid construct and a second nucleic acid construct of a composition according to claim 1.

21. The cell according to claim 20 which is a tumor cell.

22. An in vitro method comprising introduction of a first nucleic acid construct and a second nucleic acid construct of a composition according to claim 1 into a cell.

23. The method according to claim 22 wherein said cell is a tumor cell.

24. The method according to claim 23 wherein said first nucleic acid construct and said second nucleic acid construct are introduced into said cell *in vitro*.

25. The composition of claim 1, wherein said first promoter is selected from the group consisting of the HSP70 promoter, the Bcl-2 promoter, the PCNA promoter, the MDR1 promoter, the CMV promoter and the $p16^{INK4}$ promoter.